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EFFECTS OF *d*- AND *l*-AMPHETAMINE ON LOCAL CEREBRAL GLUCOSE UTILIZATION IN THE CONSCIOUS RAT[1]

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Abstract—Amphetamine, a potent sympathomimetic amine, has powerful stimulant actions in the central nervous system. These actions are believed to be related to the influence of amphetamine on release and uptake of catecholamine neurotransmitters. The [^{14}C]deoxyglucose method makes it possible to study changes in cerebral metabolic rate in different areas of gray and white matter. Because of the close relationship between metabolic rate and functional activity, this method may be used to identify specific structures in the brain in which functional activity is altered. The [^{14}C]deoxyglucose method was used to explore for changes in metabolic rate produced by *d*- and *l*-amphetamine (5 mg/kg) in forty gray and four white matter structures in normal conscious rats. *d*-Amphetamine produced increases in local cerebral glucose utilization in a number of components of the extrapyramidal motor system, as well as in some other structures known to contain dopamine-producing and/or dopaminoceptive cells. The largest increases after *d*-amphetamine administration occurred in the subthalamic nucleus and the zona reticulata of the substantia nigra. *l*-Amphetamine produced increases in some but not all of these same structures, and these were generally smaller than those observed with *d*-amphetamine. Decreases in local cerebral glucose utilization after either *d*- or *l*-amphetamine administration were found in the habenula and the suprachiasmatic nuclei of the hypothalamus. The effects in the suprachiasmatic nuclei may reflect their normal diurnal rhythm in metabolic rate. These results indicate that amphetamines may influence behavior through effects on specific regions of the brain. Only some of these regions have previously been studied as possible sites of action of amphetamine.

AMPHETAMINE, a potent sympathomimetic amine, produces marked behavioral changes in man and animals and, when administered in large doses, can induce a schizophrenia-like psychotic state in man (ANGRIST & GERSHON, 1970; GRIFFITH *et al.*, 1970). Its behavioral effects are generally believed to result from its actions on the release and re-uptake of neurotransmitters at catecholaminergic synapses in the CNS (SNYDER *et al.*, 1972). Amphetamine, for example, has been found to decrease uptake of [^{3}H]dopamine in the corpus striatum (TAYLOR & SNYDER, 1971) and to depress spontaneous firing rates of dopamine-producing cells in the substantia nigra, possibly by activation of a feedback pathway (BUNNEY *et al.*, 1975). Such evidence has implicated dopaminergic pathways as sites of action of amphetamine, but there is also evidence to indicate similar effects in noradrenergic systems (COYLE & SNYDER, 1969; BUNNEY *et al.*, 1975). Snyder and coworkers (TAYLOR & SNYDER, 1970, 1971; SNYDER, 1974) have suggested that the dopaminergic and noradrenergic actions of amphetamine might be distinguished by comparison of the relative potencies of its *d*- and *l*-isomers in any given effect. He has presented evidence that *d*-amphetamine is 7–10 times more potent than *l*-amphetamine at noradrenergic synapses but only 2–3 times more potent at dopaminergic sites (SNYDER, 1974). These relative potencies have not been uniformly confirmed; in fact, nearly opposite relative potencies have been observed (FERRIS *et al.*, 1972; HARRIS & BALDESSARINI, 1973; HEIKKILA *et al.*, 1975).

Although a number of dopaminergic pathways have been identified in the CNS (MELTZER & STAHL, 1976), the nigrostriatal and mesolimbic dopamine-pathways have been most thoroughly examined as possible sites of action of amphetamine. Some of the drug's behavioral effects, particularly the stereotyped behavior, have been associated with effects in the nigrostriatal pathway (TAYLOR & SNYDER, 1971; BUNNEY *et al.*, 1975; REBEC & GROVES, 1975). Effects in the mesolimbic system are believed to be involved in amphetamine-induced psychosis, and, in fact, because of similarities between amphetamine-psychosis and schizophrenia, abnormalities in the mesolimbic system have been suspected in schizophrenic states (SNYDER *et al.*, 1972). The effects of amphetamine in other dopamine-pathways, or, indeed, in most other systems of the CNS, have not been so thoroughly investigated.

[1] Preliminary reports of portions of this work were presented at the 7th Annual Meeting of the Society for Neurosciences, November 1977, Anaheim, CA (WECHSLER *et al.*, 1977).

The recently developed [^{14}C]deoxyglucose method has made it possible to measure the rates of glucose utilization simultaneously in all the anatomical and functional components of the CNS (SOKOLOFF *et al.*, 1977). Because of the close coupling between energy metabolism and functional activity, this method has proved useful to map localized regions of the brain with altered functional activity in various physiological and pharmacological states (SOKOLOFF, 1977). This technique has been applied to normal conscious rats treated with *d*- or *l*-amphetamine. A number of structures known to be components of dopamine-pathways, such as the caudate nucleus and substantia nigra, were found to have markedly increased rates of glucose metabolism; some components of other dopamine-pathways were unaffected; and a few structures not previously associated with catecholaminergic systems exhibited altered rates of glucose utilization.

MATERIALS AND METHODS

Animals. Normal adult male Sprague–Dawley rats weighing 350–400 g were used in all experiments. The animals were maintained on Purina Laboratory Chow and water *ad lib.* until the time of the experiments.

Materials. 2-Deoxy-D-[1-^{14}C]glucose (spec. act., 50–55 mCi/mmol) was purchased from New England Nuclear Corp. (Boston, MA). Calibrated [^{14}C]toluene, used for internal standardization of samples assayed by liquid scintillation counting, was also obtained from New England Nuclear Corp. (Boston, MA). The *d*- and *l*-isomers of amphetamine sulfate were obtained from Sigma Chemical Co. (St. Louis, MO) and Smith, Kline, and French Laboratories (Phila., PA), respectively.

Experimental procedures. Local cerebral glucose utilization was measured by the [^{14}C]deoxyglucose method described by SOKOLOFF *et al.* (1977). The animals were anesthetized with halothane and N_2O, and polyethylene catheters were inserted in one femoral artery and vein. They were then placed in a loose-fitting plaster cast and immobilized from the abdomen to the hind-legs; the head, forelegs, and thorax were unrestrained. At least 2 h were allowed for complete recovery from the effects of anesthesia. The animals were then injected intravenously with either physiological saline or 5 mg/kg of *d*- or *l*-amphetamine sulfate in normal saline. Fifteen minutes later 50 μCi of [^{14}C]deoxyglucose were administered as a pulse via the intravenous catheter, and timed arterial blood samples were then drawn during the following 45 min. The arterial blood samples were immediately centrifuged in a Beckman Microfuge B (Beckman Instrument Co., Fullerton, CA), and the plasma was separated and stored on ice until further analysis. At the end of the 45 min period the animals were decapitated, and the brains were removed as rapidly as possible and frozen in Freon XII chilled to -70°C in liquid nitrogen. The brains were then coated with chilled embedding medium (Lipshaw Manufacturing Co., Detroit, MI), stored at -70°C in plastic bags, eventually sectioned into 20 μm sections at -22°C in a cryostat, and autoradiographed along with calibrated [^{14}C]methyl methacrylate standards as previously described (SOKOLOFF *et al.*, 1977).

The arterial plasma samples were assayed for [^{14}C] deoxyglucose concentration by liquid scintillation counting with internal standardization and for glucose concentration by means of a Beckman Glucose Analyzer (Beckman Instrument Co., Fullerton, CA), also as previously described (SOKOLOFF *et al.*, 1977). Local tissue concentrations of ^{14}C were determined from the autoradiographs by densitometric analysis of the autoradiographs with a scanning microdensitometer (Gamma Scientific Corp., San Diego, CA) with an aperture of 100 μm. Local cerebral glucose utilization was calculated as previously described (SOKOLOFF *et al.*, 1977).

Statistical analyses. Local cerebral glucose utilization was measured in 40 gray and 4 white structures in 5 control animals, 5 animals treated with *d*-amphetamine, and 5 treated with *l*-amphetamine. Each structure was analyzed for statistically significant effects of the drugs by the procedure of DUNNETT (1955; 1964). This procedure is specifically designed for multiple comparisons with a single control group and is a more rigorous test for statistical significance than Student's *t* test.

RESULTS

Behavior

The control animals were all awake and alert throughout the experimental period. Both *d*- and *l*-amphetamine produced gross behavioral changes that were readily apparent in all animals receiving either drug. Despite restraint of the pelvis and lower limbs, animals treated with either isomer exhibited increased side-to-side and front-to-back movements and sniffing and exploratory behavior that began quickly after administration of the drug and persisted throughout the experimental period. The effects of *d*-amphetamine were always more prominent than those of *l*-amphetamine, and animals treated with *d*-amphetamine maintained their level of stimulation throughout the experiment whereas the behavioral effects of the *l*-isomer tended to abate somewhat toward the end of the experimental period.

Effects of d-*amphetamine on local cerebral glucose utilization*

d-Amphetamine stimulated glucose utilization in a number, though by no means all, of the gray structures of the brain examined (Table 1). Most of the structures thus affected are known sites of dopamine-producing or dopamine-receptive cells, and the most prominent effects were in components of the extrapyramidal motor system. The greatest percent increases were observed in the zona reticulata of the substantia nigra (+87%) and the subthalamic nucleus (+67%). The effects in these two structures were so pronounced that they could be visualized directly in the autoradiographs (Fig. 1). Other components of the extrapyramidal system also significantly affected were the zona compacta of the substantia nigra, the caudate nucleus, the globus pallidus, and the red nucleus. Statistically significant increases were also observed in the visual cortex, ventral nucleus of the thalamus, and area A_{13}, a hypothalamic brain structure demon-

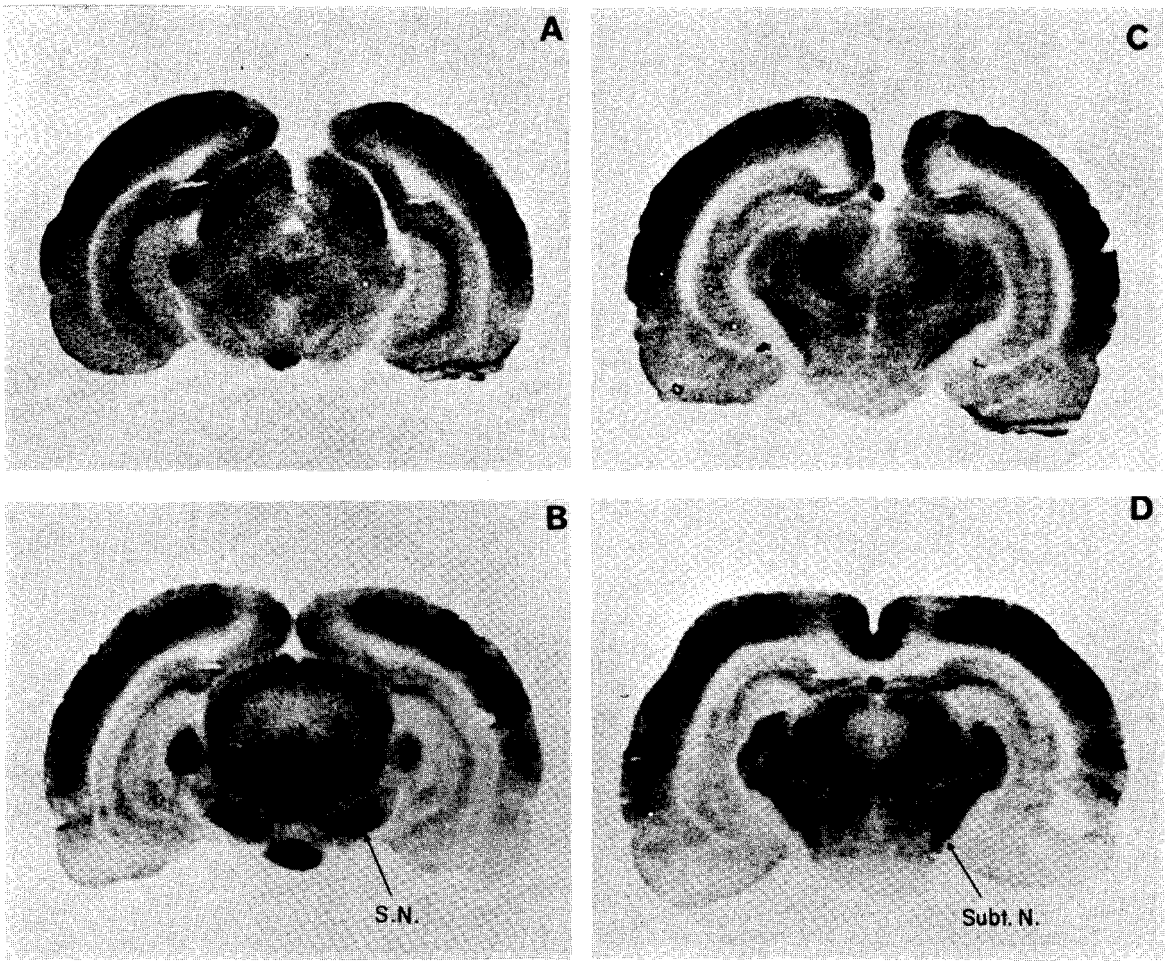

FIG. 1. Autoradiographic visualization of the effects of *d*-amphetamine on local cerebral glucose utilization in components of the extrapyramidal motor system. A and B, comparable sections from control (A) and drug-treated (B) animals at the level of the substantia nigra (S.N.). C and D, comparable sections from control (C) and amphetamine-treated (D) animals at the level of the subthalamic nucleus (Subt. N.).

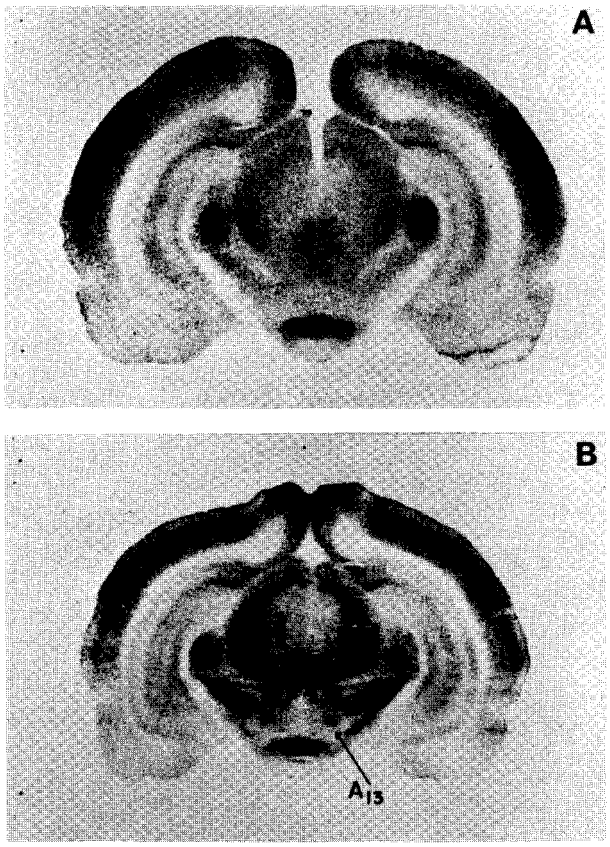

FIG. 2. Autoradiographic visualization of effects of *d*-amphetamine on local glucose utilization in area A_{13} of the hypothalamus. A and B, comparable sections from control (A) and amphetamine-treated (B) animals.

TABLE 1. EFFECTS OF *d*-AMPHETAMINE AND *l*-AMPHETAMINE ON LOCAL CEREBRAL GLUCOSE UTILIZATION IN THE CONSCIOUS RAT†

	Control	*d*-Amphetamine	*l*-Amphetamine
	Gray matter		
Visual cortex	102 ± 8	135 ± 11*	105 ± 8
Auditory cortex	160 ± 11	162 ± 6	141 ± 6
Parietal cortex	109 ± 9	125 ± 10	116 ± 4
Sensory–motor cortex	118 ± 8	139 ± 9	111 ± 4
Olfactory cortex	100 ± 6	93 ± 5	94 ± 3
Frontal cortex	109 ± 10	130 ± 8	105 ± 4
Prefrontal cortex	146 ± 10	166 ± 7	154 ± 4
Thalamus—Lateral nucleus	97 ± 5	114 ± 8	117 ± 6
Ventral nucleus	85 ± 7	108 ± 6*	96 ± 4
Habenula	118 ± 10	71 ± 5**	82 ± 2**
Dorsomedial nucleus	92 ± 6	111 ± 8	106 ± 6
Medial geniculate	116 ± 5	119 ± 4	116 ± 4
Lateral geniculate	79 ± 5	88 ± 5	84 ± 4
Hypothalamus	54 ± 5	56 ± 3	52 ± 3
Suprachiasmatic nucleus	94 ± 4	75 ± 4**	67 ± 1**
Mamillary body	117 ± 8	134 ± 5	142 ± 5*
Lateral olfactory nucleus§	92 ± 6	95 ± 5	99 ± 6
A_{13}	71 ± 4	91 ± 4**	81 ± 4
Hippocampus—Ammon's horn	79 ± 5	73 ± 2	81 ± 6
Dentate Gyrus	60 ± 4	55 ± 3	67 ± 7
Amygdala	46 ± 3	46 ± 3	44 ± 2
Septal nucleus	56 ± 3	55 ± 2	54 ± 3
Caudate nucleus	109 ± 5	132 ± 8*	127 ± 3*
Nucleus accumbens	76 ± 5	80 ± 3	78 ± 3
Globus pallidus	53 ± 3	64 ± 2*	65 ± 3*
Subthalamic nucleus	89 ± 6	149 ± 10**	107 ± 2
Substantia nigra—zona reticulata	58 ± 2	105 ± 4**	72 ± 4
Zona Compacta	65 ± 4	88 ± 6**	72 ± 3
Red nucleus	76 ± 5	94 ± 5*	86 ± 2
Vestibular nucleus	121 ± 11	137 ± 5	130 ± 4
Cochlear nucleus	139 ± 6	126 ± 1	141 ± 5
Superior olivary nucleus	144 ± 4	143 ± 4	147 ± 6
Lateral lemniscus	107 ± 3	96 ± 5	98 ± 3
Inferior colliculus	193 ± 10	169 ± 5	150 ± 8**
Dorsal tegmental nucleus	109 ± 5	112 ± 7	122 ± 6
Superior colliculus	80 ± 5	89 ± 3	91 ± 1
Pontine gray	58 ± 4	65 ± 3	60 ± 1
Cerebellar flocculus	124 ± 10	146 ± 15	153 ± 10
Cerebellar hemispheres	55 ± 3	68 ± 6	64 ± 2
Cerebellar nuclei	102 ± 4	105 ± 8	110 ± 3
	White matter		
Corpus callosum	23 ± 3	24 ± 2	23 ± 1
Genu of corpus callosum	29 ± 2	30 ± 2	26 ± 2
Internal capsule	21 ± 1	24 ± 2	19 ± 2
Cerebellar white	28 ± 1	31 ± 2	31 ± 2

† All values are the means ± S.E. of the mean for five animals.
* Significant difference from the control at the $P < 0.05$ level.
** Significant difference from the control at the $P < 0.01$ level.
§ It was not possible to correlate precisely this area on autoradiographs with a specific structure in the rat brain. It is, however, most likely the lateral olfactory nucleus.

strated by UNGERSTEDT (1971) to contain dopamine-producing cells. The effects in area A_{13} were also visible in the autoradiographs (Fig. 2). *d*-Amphetamine may also have stimulated glucose utilization in the frontal and sensory-motor cortex, but the increases observed in these structures were barely short of statistical significance at the $P < 0.05$ level.

Several structures known to contain dopaminergic synapses and dopamine-receptive cells did not appear to be affected by *d*-amphetamine. The nucleus accumbens was clearly visible in the autoradiographs of both the control and experimental animals, but its glucose consumption was unchanged. The olfactory tubercle, central amygdaloid nucleus, and area A_{10} of the ventral tegmentum, the site of origin of the mesolimbic dopamine pathway, could not be identified in the autoradiographs, presumably because their rates of glucose utilization were not sufficiently different from those of the tissues surrounding them.

Two gray structures exhibited reduced rates of glu-

cose utilization. These were the suprachiasmatic nucleus and the habenula. Neither of these areas are known to be part of any dopamine pathway. No changes were observed in any of the white structures (Table 1).

Effects of l-amphetamine on local cerebral glucose utilization

The effects of *l*-amphetamine resembled those of *d*-amphetamine, but they were less pronounced, and fewer structures were affected (Table 1). Of the structures of the extrapyramidal system that were clearly affected by *d*-amphetamine, only the caudate nucleus and globus pallidus exhibited a statistically significant increase in glucose utilization in response to *l*-amphetamine. In these structures the effects of the two isomers were quantitatively similar. There also appeared to be increases in glucose utilization in the substantia nigra and subthalamic nucleus, but these were less than those seen with *d*-amphetamine and short of statistical significance. Glucose utilization was reduced in the habenula and suprachiasmatic nuclei to the same degree as observed with *d*-amphetamine, and it was also depressed in the inferior colliculus. There were no effects in the cerebral cortical regions nor in any of the white structures.

DISCUSSION

The results of the present studies demonstrate that *d*-amphetamine in doses that produce characteristic stereotyped behavior and increased locomotor activity stimulates glucose utilization in specific regions of the brain. The effects are clearly selective and are restricted to a limited number of specific regions, most of which are known to be components of major dopaminergic pathways in the brain. Essentially all the structures of the extrapyramidal motor pathway were stimulated. These include the zona compacta and zona reticulata of the substantia nigra, caudate nucleus, globus pallidus, subthalamic nucleus, and red nucleus. The effects in the zona compacta and caudate nucleus are fully consistent with the well-established evidence that the nigrostriatal pathway is a dopaminergic system and a site of action of dopamine agonists like amphetamine (TAYLOR & SNYDER, 1971; BUNNEY *et al.*, 1975; REBEC & GROVES, 1975). Although less conclusive, there is also evidence that the globus pallidus contains significant quantities of dopamine (VEERSTEEG *et al.*, 1976) and dopamine receptors (BURT *et al.*, 1976) and is, therefore, a potential site for actions of dopamine agonists.

Less expected were the effects in the zona reticulata and the subthalamic nucleus, the most pronounced of any seen in the brain. These structures have not generally been considered components of dopaminergic systems. The zona reticulata, however, has recently been shown to be the site of termination of a feedback pathway from the caudate nucleus to the substantia nigra (BUNNEY & AGHAJANIAN, 1976), and a dopamine-sensitive adenylate cyclase, present not in the dopamine-cell bodies of the zona compacta but presumably in cells of the zona reticulata, has recently been found in the substantia nigra (GALE *et al.*, 1977). Similarly, significant quantities of dopamine (VEERSTEEG *et al.*, 1976) and dopamine-sensitive adenylate cyclase (WOLFSON *et al.*, 1977) have recently been found in the subthalamic nucleus. The present results obtained with amphetamine provide additional evidence that these two structures function in some still undefined dopaminergic systems. It should be noted, however, that the [^{14}C]deoxyglucose method measures only glucose utilization, and because of the close coupling between energy metabolism and functional activity, it serves as a marker for altered functional activity (SOKOLOFF, 1977). It is conceivable that some of the structures with increased utilization were not activated directly by amphetamine action but indirectly because they were part of a neural pathway activated elsewhere by the drug.

BROWN & WOLFSON (1978) have recently reported similar studies with [^{14}C]deoxyglucose on the effects of another dopamine agonist, apomorphine. Although they employed only the autoradiographic aspects of the method without full quantification, they were able to demonstrate in the autoradiographs increased relative densities for the same components of the extrapyramidal system shown in the present studies to have increased rates of glucose utilization in response to *d*-amphetamine. These effects were prevented by prior treatment of the animals with the dopamine-blocking agent, haloperidol, which by itself had undetectable effects except, perhaps, to increase autoradiographic density in the region of the zona compacta (BROWN & WOLFSON, 1978). The congruence of the effects with two different dopamine agonists and the prevention of effects with a dopamine-blocking drug strongly indicate that the effects in the components of the extrapyramidal motor system are consequences of the dopamine-agonistic actions of the drugs.

Not all dopaminergic pathways were stimulated by amphetamine. None of the components of the dopaminergic mesolimbic system appeared to be affected. A_{10}, the site of origin of this pathway, could not be visualized in the autoradiographs of the ventral tegmentum from both control and drug-treated animals, and the nucleus accumbens, one of its projection areas, exhibited no change in glucose utilization. WOLFSON & BROWN (1978) also failed to observe any effects of apomorphine in the mesolimbic system.

Glucose utilization was inhibited by amphetamine in two structures of the brain, the suprachiasmatic nuclei and the habenula, and both the *d*- and *l*-isomers had essentially equal effects. The changes in metabolism in the suprachiasmatic nuclei were probably unrelated to the actions of amphetamine. These nuclei have recently been found to exhibit a diurnal rhythm in their rate of glucose utilization (SCHWARTZ & GAINER, 1977), and the changes seen in the present studies may reflect differences in the

time of day between the control and experimental studies. The habenula, however, exhibits no such rhythm, and the basis of the inhibition of its glucose utilization by both *d*- and *l*-amphetamine is unclear.

The effects of *d*-amphetamine were clearly more pronounced and more diffuse than those of the *l*-isomer at the dose used in the present studies. The results are, therefore, in agreement with those of SNYDER (1974) that indicate greater potency of the *d*-isomer at both noradrenergic and dopaminergic sites. He has suggested that the adrenergic and dopaminergic actions of the drug could be differentiated on the basis of their different relative potencies in these two types of systems (SNYDER, 1974). However, inasmuch as the effects of *d*-amphetamine were confined, with relatively few exceptions, to dopaminergic systems and *l*-amphetamine was largely without stimulatory effect, there does not appear to be any basis from the present results on which to exercise such discrimination.

NAHORSKI & ROGERS (1973) have reported that *d*-amphetamine exerts in the conscious mouse a temporally biphasic effect, first an inhibition followed by a stimulation, on the glycolytic flux in the brain as a whole. In the rat, lightly anesthetized with 70% N_2O–30% O_2 and immobilized with a neuromuscular blocking agent, CARLSSON *et al.* (1975) observed an approx 40% increase in overall cerebral O_2 consumption following amphetamine administration. MCCULLOCH & HARPER (1977) observed similar stimulatory effects of *d*-amphetamine in the anesthetized baboon. In order to compare the local values of energy metabolism obtained in the present studies with the average values in the brain as a whole obtained previously, it would be necessary to obtain a mean of the local values weighted by the relative weights of the individual structures. Such weighting factors are presently unavailable for the rat brain. The present studies demonstrate that the effects of amphetamine are not generalized but selective in specific regions of the brain. It seems unlikely from the number and size of the structures affected and the magnitude of the effects that the average glucose utilization of the brain as a whole could have been very greatly affected. Indeed, comparison of the simple arithmetic means of all the gray structures indicates no significant differences in average gray matter glucose utilization between the control animals and either of the two amphetamine-treated groups. The present results are, therefore, more in agreement with those of previous studies in conscious man which failed to demonstrate any significant effects of amphetamine on average cerebral oxygen consumption (ABREU *et al.*, 1949; SHENKIN, 1951).

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